

Chronic neutrophilic leukaemia with enlarged lymph nodes and lysozyme deficiency

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SUMMARY A further case of chronic neutrophilic leukaemia is reported and compared to fourteen previously reported cases. The presence of enlarged lymph nodes as the first clinical sign and the existence of a relative lysozyme deficiency of the granulocytes were striking features.

Chronic neutrophilic leukaemia is a very rare type of leukaemia with only fourteen reported cases. The purpose of this paper is to report a case of chronic neutrophilic leukaemia with two new features, which presented with enlarged lymph nodes and showed a relative lysozyme deficiency in the neutrophil granules.

Case report

A caucasian 50-year-old man was admitted to the hospital in October 1979 with diffuse lymphadenopathy and splenomegaly.

Initial investigations showed: ESR 12 mm/h; haemoglobin 9.5 mmol/l (15.4 g/dl); platelets $230 \times 10^9/l$; WBC $10.3 \times 10^9/l$ with a normal differential cell count; IgG 15.2 g/l; IgM 1.6 g/l; IgA 4.6 g/l; no monoclonal component in serum and urine; circulating immune complexes negative; direct and indirect Coombs' test negative; uric acid 370 $\mu\text{mol/l}$ (6.2 mg/dl); Paul-Bunnell test negative; titres of antibodies against Epstein-Barr virus, *Toxoplasma gondii*, rubella, cytomegalovirus and other viruses: normal.

Chest x-ray examination revealed old inactive tuberculous lesions of the apex of the right lung. The sternal bone marrow aspirate was normal. A CT scan of the abdomen revealed the presence of enlarged paraaortic lymph nodes with a little splenomegaly. An initial lymph node biopsy from the axilla was consistent with a benign reactive lymphadenopathy with a slight polymorphonuclear infiltrate.

After one month, the lymphadenopathy worsened and there was obvious splenomegaly. The patient now complained of fever, night sweat, weakness and anorexia. Haematological examination at this time

showed: ESR 55 mm/h; WBC $11.6 \times 10^9/l$ with 87% neutrophils; proteins in serum 77 g/l with 27.9% γ globulins; IgG 22.6 g/l; IgA 4.2 g/l; IgM 2.4 g/l; no monoclonal component in serum; Coombs' test negative. Sepsis, tuberculosis, and systemic mycosis were not confirmed by extensive bacteriological tests. A cervical lymph node biopsy showed destruction of the lymphoid architecture by a predominantly neutrophilic infiltrate. Reed-Sternberg cells, fibrosis, vascular proliferation, and eosinophils were not seen. Laparotomy was refused by the patient. Three cycles of MOPP were administered from January to March 1980. The lymphadenopathy and fever partially regressed but there was no improvement of the general condition.

After seven months, the lymph nodes increased even further in size and were painful; splenomegaly was increased. The patient had a high fever but blood and urine cultures were repeatedly negative. He was treated empirically with broad spectrum antibiotics but the fever persisted.

At this stage haematological examination showed: ESR 96 mm/h; WBC $25.2 \times 10^9/l$ with 76% neutrophils, 1% eosinophils, no basophils, 14% lymphocytes, 5% monocytes, 1% LUC, 2% HPX and + 3% remainder (Hemalog-D differential cell count); haemoglobin 6.3 mmol/l (10.2 g/dl); platelets $230 \times 10^9/l$; uric acid 481 $\mu\text{mol/l}$ (8.3 mg/dl).

A high leucocyte alkaline phosphatase score at 253, a high serum vitamin B₁₂ level at 2000 pg/ml with a low serum folic acid concentration at 2.6 ng/ml were noted. Serum lysozyme activity was normal despite the increased WBC while serum lactoferrin levels were raised in relation to the leucocytosis (Table 3). A bone-marrow biopsy was mainly occupied by mature neutrophils (Fig. 1). The myelocytic-erythrocytic ratio was 17.7 with 'a

Table 1 Chronic neutrophilic leukaemia: clinical picture

Case	Age (yr)	Sex	Spleno-megaly	Adenomegaly	Treatment	Cause of death
Rathery ^{* 2} (1902)	60	M	+	— (microscopic)	Splenectomy	Postoperative (splenectomy)
Hirschfeld ^{* 2} (1904)	64	F	+	—	Arsenicals splenectomy	Postoperative (splenectomy)
Tuohy ¹ (1920)	58	F	+	—	Splenectomy	Streptococcal pneumonia
Emile-Weil	31	F	+	—	Splenectomy	Leukaemia
and See (1932) ²	27	M	+	—	Splenic irradiation	?
Exton-Smith and Chazan ³ (1957)	80	F	+	—	?	?
Tanzer <i>et al</i> ⁵ (1964)	72	M	+	—	Splenic irradiation. Busulfan	Pneumonia.
Jackson and Clark ⁶ (1965)	66	F	+	—	Busulfan	Sudden death
Rubin ⁷ (1966)	58	M	+	—	Tuberculous chemotherapy	Renal failure
					Busulfan	
Silberstein <i>et al</i> ⁸ (1974)	75	F	+	—	Splenic irradiation. Busulfan	Urinary tract infection
Shindo <i>et al</i> ⁹ (1977)	74	M	+	—	Busulfan	Blastic crisis
You and Weisbrot ¹⁰ (1979)	60	M	+	+	(microscopic) —	Haemorrhage after splenic puncture
	81	M	+	—	—	?
Barford and Jacobs ¹¹ (1980)	49	M	+	—	Busulfan	Blastic crisis
Our case (1981)	50	M	+	+	MOPP Splenectomy. Busulfan	Staphylococcal pneumopathy

* Reported in the publication of Emile-Weil and See.²
The three cases of Scott (1957)⁴ are not detailed.

Table 2 Chronic neutrophilic leukaemia blood examination: biological picture

Case	Anaemia	Platelets ($\times 10^9/l$)	WBC ($\times 10^9/l$)	Neutrophils (%)	Bone marrow	Lap	Uric Acid	Vit B ₁₂
Rathery ² (1902)	+	?	41.4	79	↑ 3 lines	ND	ND	ND
Hirschfeld ² (1904)	+	?	29	79	↑ myeloid line	ND	ND	ND
Tuohy ¹ (1920)	+	?	65	99	ND	ND	ND	ND
Emile-Weil and	+	?	35	77	ND	ND	ND	ND
See ² (1932)	—	?	40	80	ND	ND	ND	ND
Exton-Smith and Chazan ³ (1957)	+	1185	71	93	↑ 3 lines	↑	ND	↑
Tanzer <i>et al</i> ⁵ (1964)	+	?	60	96	↑ myeloid line	↑	↑	ND
Jackson and Clark ⁶ (1965)	+	160	50	95	↑ mature myeloid line	↑	ND	ND
Rubin ⁷ (1966)	+	254	69.4	98	↑ mature myeloid line	↑	↑	↑
Silberstein <i>et al</i> ⁸ (1974)	—	?	45.0	88	↑ myeloid line	↑	↑	↑
Shindo <i>et al</i> ⁹ (1977)	—	192	27.3	80	↑ myeloid line	↑	↑	↑
You and	—	144	98.4	78	↑ mature myeloid line	↑	↑	↑
Weisbrot ¹⁰ (1979)	+	183	39.7	94	↑ myeloid and megakaryocytic line	↑	↑	↑
Barford and Jacobs ¹¹ (1980)	+	420	132	96	↑ myeloid line	↑	↑	↑
Our case (1981)	+	230	25.2	76	↑ mature myeloid line	↑	↑	↑

ND = not done.

↑ = raised activity or concentration.

Table 3 Lysozyme and lactoferrin values at two WBC levels

WBC $\times 10^9/l$	Lysozyme in serum (mg/l) (normal value: <10)	Lactoferrin in serum (mg/l) (0.6 < normal value < 1.2)
27	6.7	1.0
57	6.2	3.4

predominance of mature myeloid cells. The diagnosis of chronic neutrophilic leukaemia was then established. The WBC began to rise to $70 \times 10^9/l$ with 91% neutrophils and the platelet count decreased to $136 \times 10^9/l$. The cytogenic examination

showed no Philadelphia chromosome or other aberration.

Splenectomy was performed. The spleen weighed 1 kg and there were numerous enlarged lymph nodes adjacent to the large blood vessels. Light microscopy of the spleen (Fig. 2), the lymph nodes (Fig. 3) and a liver biopsy (Fig. 4) showed a diffuse infiltration by mature polymorphonuclear cells. There was no ultrastructural abnormality of the neutrophils. Döhle bodies were absent.

Chemotherapy was started with busulfan (6 mg/day) but the patient developed a *Staphylococcus aureus* oxacillin-resistant bilateral pneumopathy with

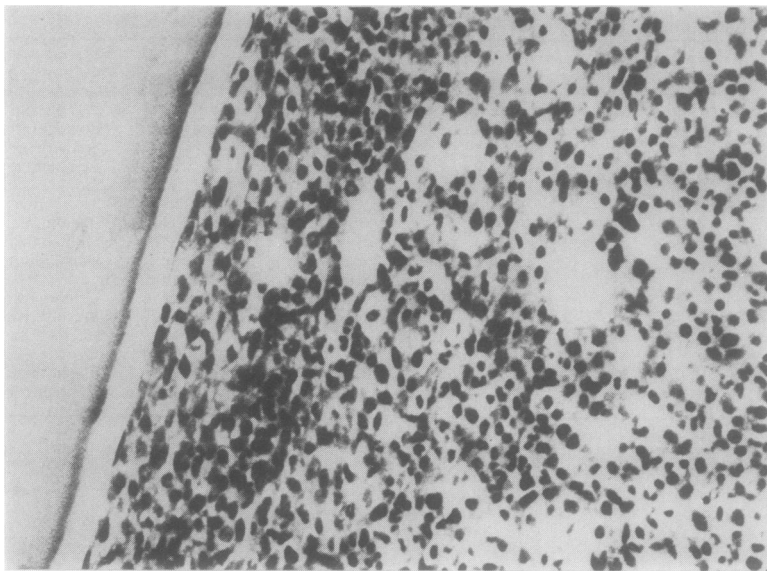


Fig. 1 *Infiltrate of neutrophils in the bone-marrow.* $\times 370$

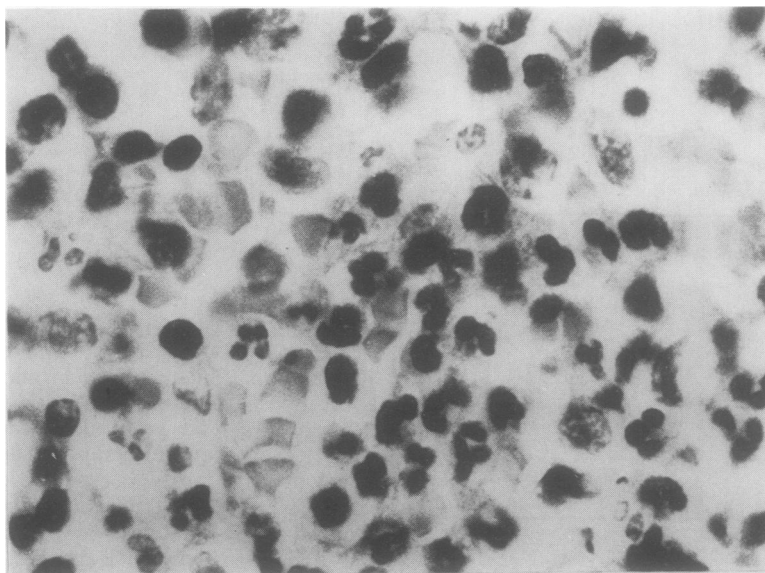


Fig. 2 *Plasma cells and mature neutrophils infiltrating the spleen.* $\times 1400$

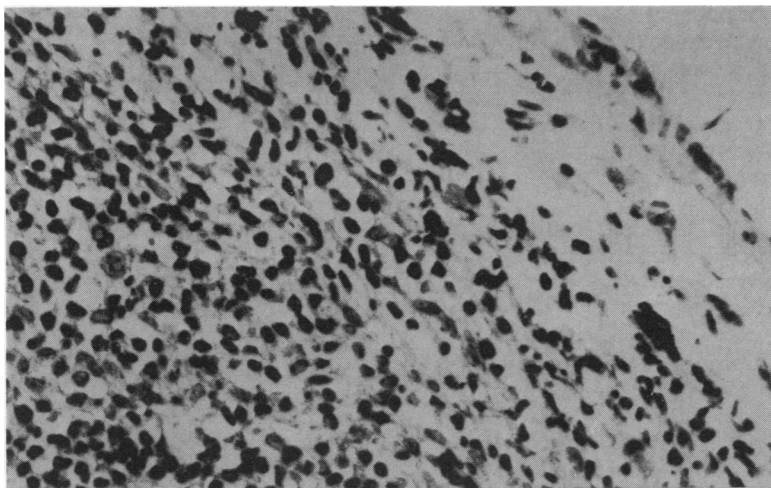


Fig. 3 Subcapsular infiltrate of neutrophils in a lymph node. $\times 490$

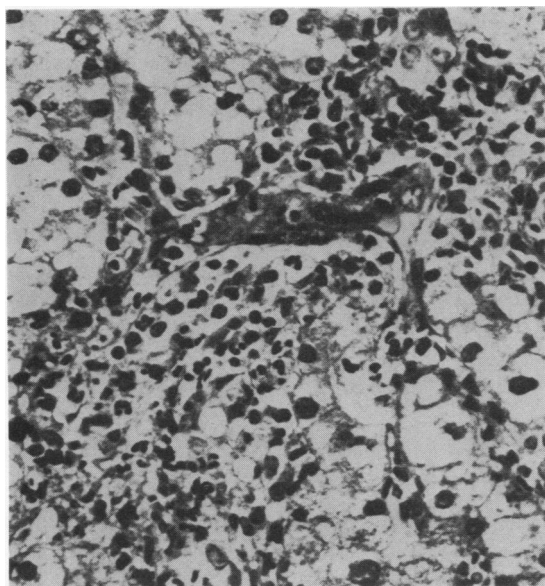


Fig. 4 Periportal infiltrate of neutrophils in the liver. $\times 350$

species; he rapidly deteriorated and died despite treatment with vancomycin. A post-mortem examination was refused.

Discussion

The diagnosis of chronic neutrophilic leukaemia is suspected on the basis of splenomegaly associated with a high white cell count, characterised by mature

neutrophil leucocytes and in the absence of any other cause for a leukaemoid reaction. The previously reported clinical and laboratory features are summarised in Tables 1 and 2.

Splenomegaly is a constant feature of the 14 previously reported cases but microscopic infiltration of lymph nodes with mature neutrophils was only present in two cases¹⁰ and enlargement of the lymph nodes has not been previously described before our case. In other respects this patient resembles those reviewed by You and Weisbrot¹⁰ but there was a relative deficiency of lysozyme contrasting with the high serum lysozyme activities reported in the case of Shindo *et al.*⁸

In general there is a significant correlation between serum lysozyme and the total mass of lysozyme-excreting cells¹²—principally the neutrophil leucocytes in this case—as well as between serum lactoferrin and the level of leucocytosis.¹³ This correlation was confined for lactoferrin in the present case but there was a discrepancy between the neutrophil counts and the serum lysozyme activities. Congenital or acquired abnormalities of neutrophils have been described: lactoferrin deficiency due to absence of specific granules in neutrophils¹⁴; peroxidase deficiency with absence of or abnormally depleted azurophilic granules¹⁵ and other enzymatic deficiencies of neutrophilic granules.¹⁶ Such deficiencies have not been reported in chronic neutrophilic leukaemia but it is tempting to speculate that this has occurred in the present case.

The absence of lysozyme may predispose to an increased susceptibility to bacterial infection. Lysozyme has a bacteriolytic action by splitting a

mucopolysaccharide component of the bacterial cell wall. Moreover, splenectomy, which is often performed in chronic neutrophilic leukaemia may predispose to *D pneumoniae*, *Neisseria meningitidis*, *Escherichia coli*, *Haemophilus influenzae* and *Staphylococcus aureus* septicaemic.¹⁷ This may be due to reduced serum concentrations of IgM¹⁸ and of properdin and tuftsin.¹⁹

It is likely that the terminal staphylococcal pneumonia despite specific chemotherapy may be attributed in part to the reduced lysozyme activity and postsplenectomy dysfunction.

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References

- ¹ Tuohy EL. A case of splenomegaly with polymorphonuclear neutrophil hyperleukocytosis. *Am J Med Sci* 1920;160:18-25.
- ² Emile-Weil AN, See G. La leucémie myélogène à polynucléaires neutrophiles. *Presse Méd* 1932;40:1071-4.
- ³ Exton-Smith AN, Chazan AA. Myeloproliferative syndrome presenting as "neutrophilic leukaemia." *Proc Roy Soc Med* 1957;50:510-1.
- ⁴ Scott RB. Leukaemia: chronic myeloid leukaemia. *Lancet* 1957;i:1099-103.
- ⁵ Tanzer J, Harel P, Boiron M, Bernard J. Cytochemical and cytogenetic findings in a case of chronic neutrophilic leukaemia of mature cell type. *Lancet* 1964;i:387-8.
- ⁶ Jackson IMD, Clark RM. A case of neutrophilic leukaemia. *Am J Med Sci* 1965;249:72-4.
- ⁷ Chronic neutrophilic leukemia. *Ann Intern Med* 1966;65:93-100.
- ⁸ Silberstein EB, Zellner DC, Shivakumar BN, Burgin LA. Neutrophilic leukemia. *Ann Intern Med* 1974;80:110-1.
- ⁹ Shindo T, Sakai C, Shibata A. Neutrophilic leukaemia and blastic crisis. *Ann Intern Med* 1977;87:66-7.
- ¹⁰ You W, Weisbrot IM. Chronic neutrophilic leukemia. Report of two cases and review of the literature. *Am J Clin Pathol* 1979;72:233-42.
- ¹¹ Bareford D, Jacobs B. Chronic neutrophilic leukaemia. *Am J Clin Pathol* 1980;73:837.
- ¹² Hansen NE. Lysozyme in haematology: pathophysiology and clinical use. *Scand J Haematol* 1975;14:160-5.
- ¹³ Malmquist TJ, Hansen NE, Karle H. Lactoferrin in haematology. *Scand J Haematol* 1978;21:5-8.
- ¹⁴ Breton-Gorius J, Mason DY, Buriot D, Vilde JL, Griscelli C. Lactoferrin deficiency as a consequence of a lack of specific granules in neutrophils from a patient with recurrent infections. *Am J Pathol* 1980;99:413-28.
- ¹⁵ Bainton DF. Abnormal neutrophils in acute myelogenous leukemia: identification of subpopulations based on analysis of azurophil and specific granules. In: Bessis M, Brecher G, eds. *Unclassifiable leukemias*. Berlin, Heidelberg, New York: 1975:191-9.
- ¹⁶ Rausch PG, Pryswansky KB, Spitznagel JK, Herion JC. Immunocytochemical identification of abnormal polymorphonuclear neutrophils in patients with leukemia. *Blood Cells* 1978;4:369-76.
- ¹⁷ Krevit W, Giebink GS, Leonard A. Overwhelming postsplenectomy infection. *Surgical clinics of North America* 1979;59:223-32.
- ¹⁸ Eichner ER. Splenic function: normal, too much and too little. *Am J Med* 1979;66:311-9.
- ¹⁹ Heier HE. Splenectomy and serious infections. *Scand J Haematol* 1980;24:5-12.

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